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Although lead exposure has had a dramatic reduction over the past several decades, Canadians are still subject to low chronic exposure. Low exposure levels are difficult to measure, but it is still important to understand their effect. The O'Flaherty model of lead kinetics was developed as a way to approximate lead exposure and lead kinetics within the human body. Previous model studies have focused on adult men with high workplace lead exposures. In this study, a sample of 263 individuals of various ages from the Greater Toronto Area was selected to test the accuracy of the current version of the O'Flaherty model to populations with low chronic lead exposure. Bone and blood lead concentrations were measured on participants from ages 1 to 85. With this information, adjustments to the O'Flaherty model were made to make it more applicable for the general population.

Physiologically Based Modeling of Lead Kinetics: A Pilot Study Using Data from a Canadian Population

John W. MacMillan[a], Sepideh Behinaein[b], David R. Chettle[b], Mike Inskip[b], Fiona E. McNeill[b], William I. Manton[c], Norm Healey[d], Mandy Fisher[e], Tye E. Arbuckle[e], David E.B. Fleming[a*]

*corresponding author

[a] *Physics Department, Mount Allison University, Sackville, New Brunswick E4L 1E6 Canada*

[b] *McMaster University, Hamilton, Ontario, Canada*

[c] *University of Texas at Dallas, Dallas, Texas, USA*

[d] *Azimuth Consulting Group, Vancouver, British Columbia, Canada*

[e] *Health Canada, Ottawa, Ontario, Canada*

The Canadian population is currently subject to low, chronic lead exposure, and an understanding of its effects is of great significance to the population's health. Such low exposure is difficult to measure directly; approximation by physiologically based modeling may provide a preferable approach to population analysis. The O'Flaherty model of lead kinetics is based on an age-dependent approach to human growth and development, and devotes special attention to bone turnover rates; because lead is a bone-seeking element, the model was deemed ideal for such an analysis. A sample of 263 individuals of various ages from the Greater Toronto Area was selected for evaluation of the applicability of the current version of the O'Flaherty model to populations with low lead exposure. For each individual, the lead exposure input was calibrated to match the cortical bone lead output to the individual's measured tibia lead concentration; the outputs for trabecular bone, blood, and plasma lead concentration obtained from these calibrations were then compared to the subjects' measured calcaneus, blood, and serum lead concentrations, respectively. This indicated a need for revision of model parameters; those for blood lead binding and lead clearance from blood to bone were adjusted, and new output was obtained in the same fashion as before. Model predictions for trabecular lead concentration did not agree with measurements in the calcaneus. The output for blood and plasma lead concentrations were highly scattered and, on an individual level, inconsistent with corresponding measurements; however, the general trends of the output matched those of the measurements reasonably well, indicating that the revised blood lead binding and lead clearance parameters may be useful in future studies. Overall, the analysis showed that with the model revisions discussed herein, the model should be a useful tool in the analysis of human lead kinetics and body burden in populations characterized by low, chronic exposure to lead from the general environment.

INTRODUCTION

Lead toxicity adversely affects various organ systems throughout the body, and is of significant concern to environmental health.[1] Although the effects of acute, high exposure to lead

are well documented,[2] those of lower and chronic exposure are much less certain. In recent years, regulation of human lead exposure has greatly increased, but trace amounts still remain in the environment, particularly as a result of previous use – for example, in old lead pipes and lead-based paint. As such, an understanding of the effects of low, chronic exposure is of great significance to today's society. This understanding requires an accurate description of the distribution of lead in the human body, which is difficult to measure directly in humans with very low lead body burdens. An ability to accurately connect lead exposure to distribution in the body would, as one key benefit, better inform future public health policy recommendations concerning lead.

A variety of computer-based lead kinetic models exist including the Integrated Exposure Uptake Biokinetic (IEUBK) model,[3] the Leggett model,[4] and the O'Flaherty model.[5] The IEUBK model is dedicated solely to lead kinetics in children, and therefore was not a good choice for the current study. The Leggett model does not explicitly consider physiological parameters which can vary over time, and between women and men. The O'Flaherty model appeared to be best suited to our current project. The O'Flaherty model is a physiologically based model of lead kinetics that pays special attention to time-dependent processes, particularly bone formation rate.[5] Previous studies of chronic lead exposure using this model have focused on adult men with significant occupational exposure [6] or cynomolgus monkeys.[7] These studies have not been able to address the kinetics and effects of lead in women and children, who are known to be especially vulnerable to lead toxicity.[2,8,9] Despite current environmental regulations of lead exposure, children can still ingest potentially harmful amounts of lead from numerous sources, including soil, dust, infant formula, and lead-based paint.[10,11] While adult women are subjected to fewer sources of lead exposure, many of them were born before recent advances in exposure regulation, and carry relatively large body burdens of lead; when these women are pregnant, this body burden can become a health issue to both the fetus and the mother.[8] In addition, Silbergeld, Schwartz and Mahaffey [9] have suggested that menopause is generally accompanied by a substantial release of bone lead into the blood – from which it can reach other tissues – and the lead remaining in the bone may aggravate postmenopausal osteoporosis.

In this study, the O'Flaherty model of lead metabolism is applied to a sample of 263 environmentally exposed subjects from the Greater Toronto Area.[12] This study sample provides a unique opportunity to assess exposure to lead from the general environment, in a contemporary urban Canadian setting. Notably, the study includes measurements of whole blood lead, serum lead, tibia lead, and calcaneus lead concentrations. These represent important "pools" or "compartments" of lead in the human body, and allow for the comparison of real data against output from the O'Flaherty model. In this study, modeled chronic exposures are first adjusted for each participant, until the modeled cortical bone lead output acceptably approximates the participant's tibia lead concentration as measured by bone lead X-ray fluorescence. Next, the participants' measured calcaneus, blood, and serum lead concentrations are compared to corresponding model output. Parameters in the model are revised to improve agreement between

its output and observation. Finally, the model application to the subjects is repeated with revised parameters, and the resulting output compared to the measured data from the population.

METHODS

General Considerations

The version of the O'Flaherty model employed in this study explicitly considers the following biocomponents: whole blood, plasma, liver, kidney, other well-perfused tissues, trabecular bone, cortical bone (metabolically active and diffusion regions), and other poorly-perfused tissues. A schematic representation of how it models lead kinetics through these components is presented in Figure 1. Many variables in the model, including tissue and organ volumes, body weight, and cardiac output, are dependent on age; these variables change over (modeled) time according to curves that can be adjusted by changing specific input parameters. Full details of the model construction are provided elsewhere.[13] The version of the model (July, 1997) used in this study was written in Microsoft C++, and will be referred to here as the physiologically-based lead kinetic model (PBKM).

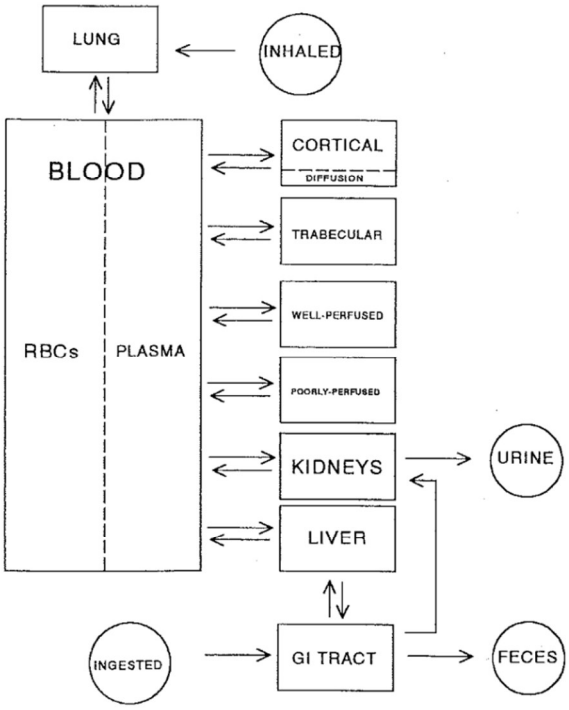

FIG. 1. Schematic representation of the O'Flaherty model of human lead metabolism.[6]

Lead is a bone-seeking element. In the human body, the majority of retained lead is stored in bone, where it can remain for years.[14] As such, any reasonably accurate model of lead metabolism must respectably capture bone lead kinetics. The O'Flaherty model describes bone in terms of two types – cortical and trabecular – and further divides cortical bone into metabolically active and quiescent regions. Each of these regions is associated with a different type of lead

metabolism; metabolically active bone is associated with modeling and remodeling, and quiescent bone undergoes a slow exchange of lead and calcium ions both within itself and with blood. Trabecular bone lead metabolism is modeled similarly to that of metabolically active cortical bone; no ion exchange is considered for this bone type. Each type of bone is also subdivided into juvenile and mature bone, each with different modeled lead kinetics; ion exchange in juvenile bone is not considered by the model, as it is negligible relative to lead kinetics arising from metabolically active processes.[6] The ratio of juvenile bone to mature bone is dependent on age, and all bone is considered to be of the mature type by the age of 25.

The participants in the current study were recruited as a convenience sample of the general population in Toronto, Ontario, Canada.[12] The overall study was designed to assess current exposure to lead in an urban Canadian population having no known exposure other than through "background" levels in the general environment. Subjects ranging from ages 1 to 83 years were recruited through St. Joseph's Hospital in Toronto. The study protocol was approved by the Research Ethics Boards of Health Canada (2009-0001), St. Joseph's Health Centre in Toronto (2008-033), McMaster University (09-121), and Mount Allison University (2013-024). Three types of informed consent forms were used in the study: consent was obtained from subjects 16 years or over, assent from children 7-15, and parent consent for children under 7. In total, 128 female subjects and 135 male subjects took part in the study. Therefore, a total of 263 participants were available for modeling. Biological indices of lead exposure were measured in the population between 2009 and 2011: subjects were measured for whole blood lead concentration, serum lead concentration, tibia bone lead concentration, and calcaneus bone lead concentration. No environmental lead exposure data (such as intake of lead through water, food, or air) were available for the subjects. Model default values for environmental lead exposure were therefore used, with individual adjustments made as described below under Initial Application of Model. Lead concentrations in bone were measured using a clover leaf K-shell x-ray fluorescence technique.[15,16] The bone lead measurement involves a small effective dose of ionizing radiation, ranging from < 1 μSv to < 10 μSv,[15] an amount less than the effective dose received from a single dental x-ray or chest x-ray. Before running the model, the ratio of serum lead concentration to blood lead concentration was calculated for each participant. It was found that a plot of serum lead to blood lead expressed as a percentage was a function of the order in which the samples were collected, with the ratios declining over the first 75 collections and stabilizing thereafter. We attribute the initial high values to difficulty in establishing clean techniques. The ratios measured over the stable period had an upper bound of 0.35%. Accordingly we rejected all serum values associated with serum to blood lead ratios greater than 0.35% on the grounds they had been contaminated during collection. Additionally, a smaller number of participants were excluded due to serum lead analysis not having been performed. This left 177 participants with accepted serum lead concentration measurements. 262 of the 263 participants had blood lead measurements performed.

As plasma is composed of both serum and clotting factors, the plasma and serum lead concentrations of any given individual will not be identical. However, any differences between the two were considered negligible relative to the uncertainty of the serum lead measurements used in this study; in lieu of serum being modeled as a separate tissue compartment from plasma, the model output for plasma lead concentration was used as a good approximation of the measured serum lead concentration.

Preparation of Model Input Files

An input file was created in PBKM for each participant. The file was selected for female or male, depending on the individual participant. The age, in years, at which integration was to start (TSTART) was set to 0 in all of these files. Each participant's date of birth and age at measurement (in years, rounded to the nearest 0.01 yr) were entered into the participant's input file as the year of birth (YOB) and the age at which integration was to stop (TSTOP), respectively. Certain curve constants for hematocrit (HCT), weight (WCHILD, WADULT, and LAMBDA), and bone formation rate (CUTOFF) were set according to the default values in PBKM depending on the participant's sex. In general, the integration step length (CINT, in years) was set to 0.05 for participants under the age of 13, 0.1 for those between the ages of 13 and 30, and 0.2 for those over 30. However, when the total integration length (TSTOP – TSTART) was not an integer multiple of CINT, the integration continued beyond TSTOP until it reached the end of a step, i.e. an integer multiple of CINT. To accommodate this, CINT values of 0.30, 0.25, 0.15, or 0.10 were used for participants over 30 to keep the difference between their age and the integration end point below 0.1 yr. Similarly, CINT values of 0.05 or 0.15 were used for some participants between 13 and 30 years of age, in order to keep this end point within 0.05 yr of their age. Due to a limitation in the number of available integration steps, it was not always possible to keep the end point within the desired range; in these cases, the difference was kept as low as possible. Potential differences in PBKM output for cortical bone lead concentration (CCB, in mg/L), trabecular bone lead concentration (TCB, in mg/L), and blood lead concentration (CB, in mg/L) arising from this case-by-case modification of CINT were tested by running the model with different CINT values on the same participant's data for various participants, each of whose model run end points were the same for all tested values. The differences in all of these output values based on CINT were found to be negligible. As such, it is highly unlikely that the different interval lengths would have caused any significant errors in the results.

Revision of Blood Lead Binding Constants

O'Flaherty and Reponen [13] suggest that the model parameters for the maximum lead binding capacity of erythrocytes (BIND, in mg Pb/L cell) and their half-saturation binding constant (KBIND, in mg Pb/L cell) may need to be changed based on new experimental information. In the model, blood lead concentration (CB) is a function of plasma lead concentration (CPLASMA), hematocrit (HCT), and three constants (BIND, KBIND, and G,

where G is the ratio of unbound erythrocyte lead concentration to plasma lead concentration). For a given individual in this study, CB, CPLASMA, and HCT were known from measurement, leaving the constants BIND, KBIND, and G to be solved. No other exposure information was required at this stage. New values for the constants were determined by fitting the model expression for CB in terms of BIND, KBIND, G, HCT, plasma fraction of whole blood by volume (PLASMA, equivalent to 1 – HCT), and plasma lead concentration (CPLASMA, in mg/L).[13] This was done according to the least-squares method while varying BIND, KBIND, and G to achieve the optimal fit to the measured data. Since hematocrit data were available from this study, the equation used the participants' measured hematocrits (instead of the default model hematocrit values) as input. The equation was as follows:

$$CB = PLASMA \times CPLASMA + HCT \times CPLASMA \times (G + BIND / (KBIND + CPLASMA))$$

The best fit value of G was found to be very similar to the original default value in the model. The best fit values for BIND and KBIND were substantially reduced relative to the default model values. The results of this fitting ($r^2 = 0.75$) are shown in Fig. 2, and the fitted parameter values are shown and compared to the original default model parameters in Table 1. The new values for all three parameters were then used in all subsequent model input files.

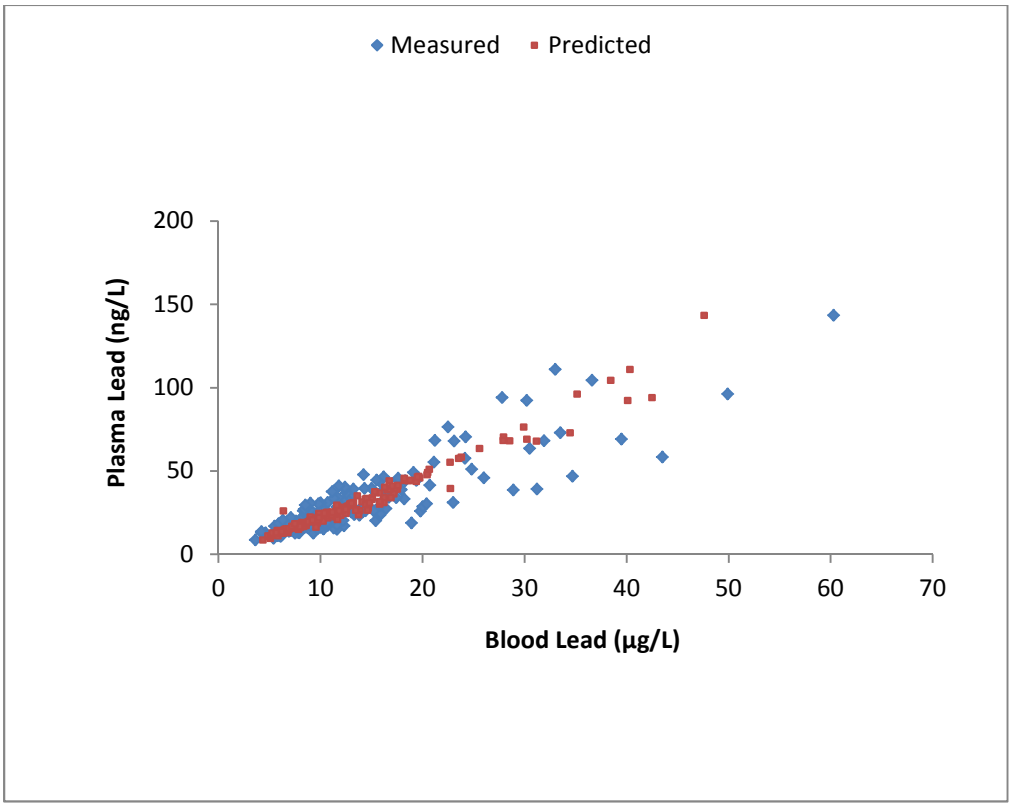

FIG. 2. Plasma lead concentration as a function of blood lead concentration – as measured and as predicted by the model equation using the revised values of BIND, KBIND, and G.

TABLE 1
Original and Revised Blood Lead Binding Constants

Parameter	Original Value	Revised Value
BIND (mg Pb/L cell)	2.7	0.437
KBIND (mg Pb/L cell)	0.0075	0.000372
G	1.2	1.19

Initial Application of Model

The model was first run for each input file with all input variables not mentioned previously left at their default values.[13] From this first run, the modeled total bone weight (WBONE, in kg) and total bone volume (VBONE, in L) were obtained, and the average bone density (DBONE, in kg/L or g/mL) was calculated as WBONE/VBONE as per the model.[13] The bone density was therefore age-dependent, and taken directly from the model using its default parameters. No attempt was made to introduce individual-specific refinements to this modeled bone density. It is important to note that the measured tibia and calcaneus lead concentrations (and their uncertainties) were provided in μg Pb/g bone mineral. However, CCB and TCB are provided from model output in mg Pb/L wet bone.[5] In order to convert the observed bone lead concentrations and uncertainties from μg Pb/g bone mineral to mg Pb/L wet bone for each participant, the measured values were multiplied by that participant's DBONE value and the documented mass ratio of bone mineral to wet bone for the appropriate bone type.[17] Measured blood and serum lead concentrations were also converted to mg/L for comparison to model output CB and CPLASMA, respectively.

The next step in the analysis was a calibration of the model input for lead exposure specific to each individual participant. Individual exposure histories were unknown, but the model requires exposure input as a function of time. An exposure history was created for each individual in order to produce agreement between model output and observation with respect to tibia lead concentration. Tibia lead concentration was selected as the calibration endpoint since it was the best available index of cumulative exposure for the study participants.[18] Exposure was delivered in a continuous fashion for each variable described below. For a given individual, the model treats water lead intake as uniform over time, while food lead intake declines from a pre-1970 rate to a current rate, and air lead intake declines from a pre-1975 rate to a current rate.[13] For each participant's input file, the model input for drinking water lead concentration (CWATER, in mg/L) was adjusted, and the model re-run, until the CCB output was within 0.05 mg/L of the observed tibia lead concentration in that participant. (Note that if the observed tibia lead was negative, the reading was simply treated as zero at this stage. Due to the mathematical fitting of bone lead energy spectra and count statistic considerations, it *is* possible for the bone lead measurement technique to return negative concentrations,[18] and these results are normally retained.) The decision to adjust water concentration first was based on the assumption that this exposure variable would be the most likely to show significant differences between individuals. The model, however, treats all lead within the body in the same way, regardless of the original

source. If agreement within 0.05 mg/L could not be achieved while keeping CWATER positive, CWATER was set to 0 and the model input for the contemporary average adult rate of ingestion of lead in food (RFOOD2, in µg/da) was adjusted. If setting both CWATER and RFOOD2 to 0 still resulted in a CCB value that was too large, both CWATER and RFOOD2 were kept at 0 and the model input for the current concentration of lead in ambient air (CAIR2, in mg/m^3) was adjusted, and so on for the pre-1970 average adult rate of lead ingestion via food (RFOOD1, in µg/da) and the pre-1975 ambient air lead concentration (CAIR1, in mg/m^3). If an appropriate value of CCB was reached, or if CCB was still too high after setting all of these input values to 0, calibration was ended and the final output values of CB, CCB, and TCB were obtained and recorded. For future analysis, the values of CWATER, RFOOD2, CAIR2, RFOOD1, and CAIR1 used to obtain the final model output for each participant were also recorded. During this procedure, if the model output for CB was negative in any run for which CCB was too high, the value being adjusted at that point in the calibration (CWATER, RFOOD2, CAIR2, RFOOD1, or CAIR1) was changed until the CB output was less than 10^{-4} mg/L and neither CB nor TCB was negative, at which point the final values of CB, CCB, and TCB were recorded. This was done to keep the model output realistic. (In lowering modeled lead exposures, CB was always found to be the first of the three output lead concentrations to become negative. This negative model output likely arose from the way in which renal excretion of lead is modeled, which is detailed in the Discussion.)

The model does not output CPLASMA directly; this value was calculated outside the model for each participant from his or her CB output, HCT input, and the revised values of BIND, KBIND, and G.

The above procedure was also performed for all data while leaving BIND, KBIND, and G at their default model values. As expected, these trials were not able to reproduce as effectively the observed relationship between plasma lead and blood lead concentrations. All further model trials were therefore performed using the revised values of BIND, KBIND, and G.

Additional Revision of Model Parameters

Both sets of results indicated that changing CWATER had a dramatic effect on the ratio of TCB to CCB output from the model. We were curious whether eliminating any individual-level variation in the modeled CWATER might improve model output. The above procedure was therefore repeated a third time. The revised values of BIND, KBIND, and G were used, and CWATER was left at its default value of 0.005. (RFOOD2, then, was the first variable to be changed in calibrating CCB to the tibia lead concentration of each participant.) For this model configuration, a few of the participants' tibia lead concentrations could not be "reached" by CCB, using the previously described procedure, without raising RFOOD2 above RFOOD1. This would violate the model's reasonable assumption that food lead intake decreased after 1970, so the default value of RFOOD1 (200) was treated as a maximum for RFOOD2. When this maximum was reached, further increases to CCB were made by increasing CAIR2 – to a

maximum of the default value of CAIR1 (0.002) for similar reasons. The only participants whose tibia lead concentrations were higher than their maximum possible CCB outputs obtainable by this method were born after 1995, and changing the values of RFOOD1 and CAIR1 had very little effect on their CCB values. Therefore, no further changes were made to the input parameters for these participants; their data were considered anomalous, and their corresponding CCB, TCB, and CB outputs were recorded at maximum CCB. This approach was not found to improve the overall accuracy of the model results; all further model trials were therefore performed by changing CWATER first, as before.

An attempt was then made to create a better fit to the measured blood and serum lead concentration data by altering the modeled bone formation rate (BFR). In the model, bone formation rate is calculated as a function of several input and calculated variables; one of these input variables, BASE, was reduced in order to lower BFR. A representative sample of 20 of the participants was obtained by randomly sampling 20 out of the population until the sample means and medians of their measured cortical bone and blood lead concentrations matched those of the population to within a factor of 1.25. The same model run procedure as before was then performed on this sample with BASE reduced by a factor of 3, by a factor of 5, and by a factor of 100. Although this produced some changes in TCB, none of these reductions produced significant differences in CB or CPLASMA – in fact, many of the sampled participants' modeled lead exposure histories were similar to those used before reducing BASE.

Finally, the model was altered by increasing the modeled lead clearance from blood to bone (P0, in cm^3/day) by factors of 5, 10, and 15, performing the model run procedure on the data from the same sample of 20 participants as before. Increasing P0 by a factor of 15 (from 0.02 to 0.3) was found to produce sample means and medians of CB and CPLASMA, as well as an average ratio of CB to CCB, that approximated the corresponding values from the measured data reasonably well; the model run procedure was then performed on the data from all 263 participants.

RESULTS

Refinement of Model

The default blood lead binding constants produced modeled blood lead output that was too high, whereas the revised constants produced output closer to the measured data. However, both sets of results indicated a need for further model refinement. In particular, the modeled blood and plasma lead concentrations were too large (even with the revised blood lead binding constants), indicating further changes were required to produce more accurate model output. This was accomplished through the modification of the P0 parameter to a revised value of 0.3.

Determination of Modeled Plasma (Serum) Lead

The plasma (serum) lead concentrations calculated from the model output for blood lead concentrations are shown and compared to the corresponding measured concentrations in Fig. 3. While the measured data are reasonably approximated by the model (aside from some scatter in the former, which is also visible from Fig. 2), the modeled blood and plasma lead concentrations have much greater ranges than the corresponding measured data. As the input for each participant was calibrated to match output from the cortical bone lead concentration to the measured tibia concentration, this effect is likely due to uncertainties in the measurement of tibia concentration. A tibia lead concentration measurement higher than the actual value would result in a model calibration with higher lead intake input parameters and, therefore, higher blood and plasma lead concentration output. (The curve in the modeled data seen at higher blood lead concentrations in Fig. 3 arises from the way in which the model relates blood and plasma lead; at higher blood lead concentrations, the red blood cells approach their maximum lead binding capacity, and a greater fraction of blood lead is contained in the plasma. The measured relationship between blood and serum lead concentrations most likely appeared linear in this data set because the participants' blood lead concentrations were too low to result in such a "saturation" of the red blood cells.) Nonetheless, revision of the blood lead binding constants yielded a modeled relationship between blood and serum lead that closely approximated the observed relationship.

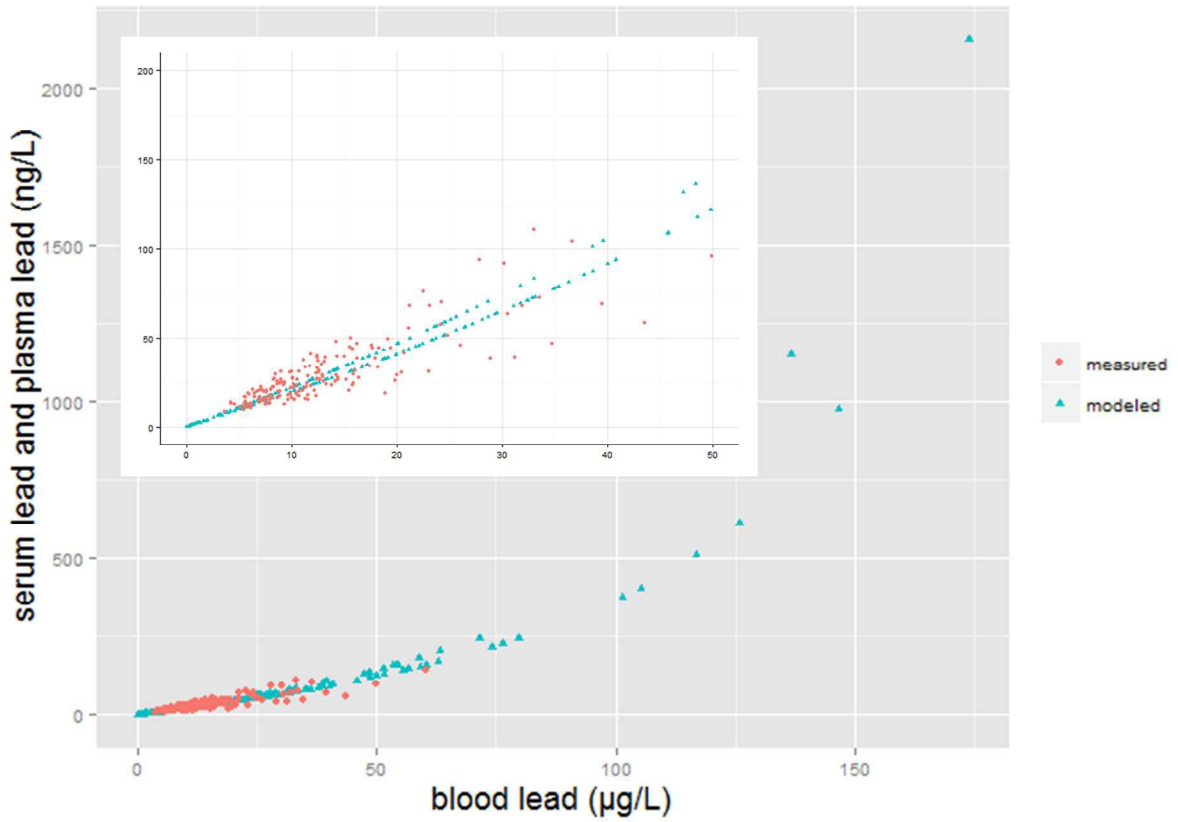

FIG. 3. Measured serum lead and modeled plasma lead concentration as a function of blood lead concentration.

General Results

The final observations and model output for tibia (cortical bone), calcaneus (trabecular bone), blood, and serum (plasma) lead concentrations are shown in Figs. 4, 5, 6, and 7, respectively. In every case investigated for both observed and modeled data, the data distributions were found to be inconsistent with a normal distribution. As assessed by the Shapiro-Wilks test, the closest approach to a normal distribution was found from the observed tibia lead concentrations. Although the data are highly scattered in the latter three graphs, and the model output for trabecular lead concentration was, overall, lower than the observed calcaneus lead concentration (see Discussion), the revised model reasonably approximated the general trends of the measured blood and serum lead data. This is further illustrated in Table 2, which shows the mean, median, and geometric mean observed tibia, blood, and serum lead concentrations from all participants, and compares them to the corresponding values from the model output. These results were obtained using the revised values of BIND, KBIND, and G, both before and after the additional revision of P0 (see Methods). The standard errors of the mean and geometric standard deviations are provided, where available. The geometric mean for measured cortical (tibia) bone is not provided since negative values were included in this data set. Standard errors and standard deviations from the original model values are not provided since the full model output was not retained at this stage.

For all three tissue compartments in Table 2, the *mean* model values do not match the corresponding measured means, even after model revision. This discrepancy is partially due to the fact that participants with negative tibia lead concentrations (of which there was a significant number; see Fig. 4) were modeled as having very low, but positive, cortical bone lead concentrations (see Methods). In general, this approach resulted in *higher* mean modeled cortical bone lead concentrations, higher mean modeled lead body burdens, and therefore, higher mean modeled blood and serum lead concentrations. As such, there is a residual discrepancy because of the positive bias introduced by the way negative tibia lead measurements had to be treated. Additionally, a moderate number of very high measured tibia lead values translated to very high modeled cortical bone lead values, producing high modeled blood and serum results. At the same time, the treatment of the negative measured tibia lead concentrations resulted in a large number of very low modeled cortical bone values and extremely low (less than 1 μg/L) modeled blood lead values. This specific collection of extremely low modeled blood lead values resulted in *geometric mean* modeled blood and serum values which were *lower* than those for the corresponding measured results. Also, as noted above, none of the observed or modeled data sets were consistent with a normal distribution. For all of these reasons, the *median* values in Table 2 should be considered better indicators of model performance (both before and after revision of P0). From the median results, it is clear that the revised model is much improved over the original model with respect to blood and serum concentrations. Median modeled results closely reflect median measured values, as demonstrated by Table 2. In summary, when individually

modeled exposures were used to fit to tibia lead measurements, the revised model gave good agreement between measured blood and serum median values and their modeled equivalents.

TABLE 2
Mean, Median, and Geometric Mean Measurements and Model Output Parameters for Bone and Blood Lead Concentration Before and After Revision of P0

Tissue Compartment	Parameter	Measured Value	Original Model Value	Revised Model Value
Cortical bone (mg/L)	Mean (SE)	3.2 (0.5)	5.1 (-)	5.4 (0.3)
	Median	3.3	3.4	3.5
	Geometric Mean (GSD)	-	-	3.4 (2.7)
Blood (µg/L)	Mean (SE)	13 (0.5)	48 (-)	19 (1.6)
	Median	11	39	11
	Geometric Mean (GSD)	11 (1.7)	-	3.4 (21)
Serum or Plasma (ng/L)	Mean (SE)	30 (1.5)	210 (-)	61 (11)
	Median	24	95	22
	Geometric Mean (GSD)	26 (1.7)	-	7.5 (23)

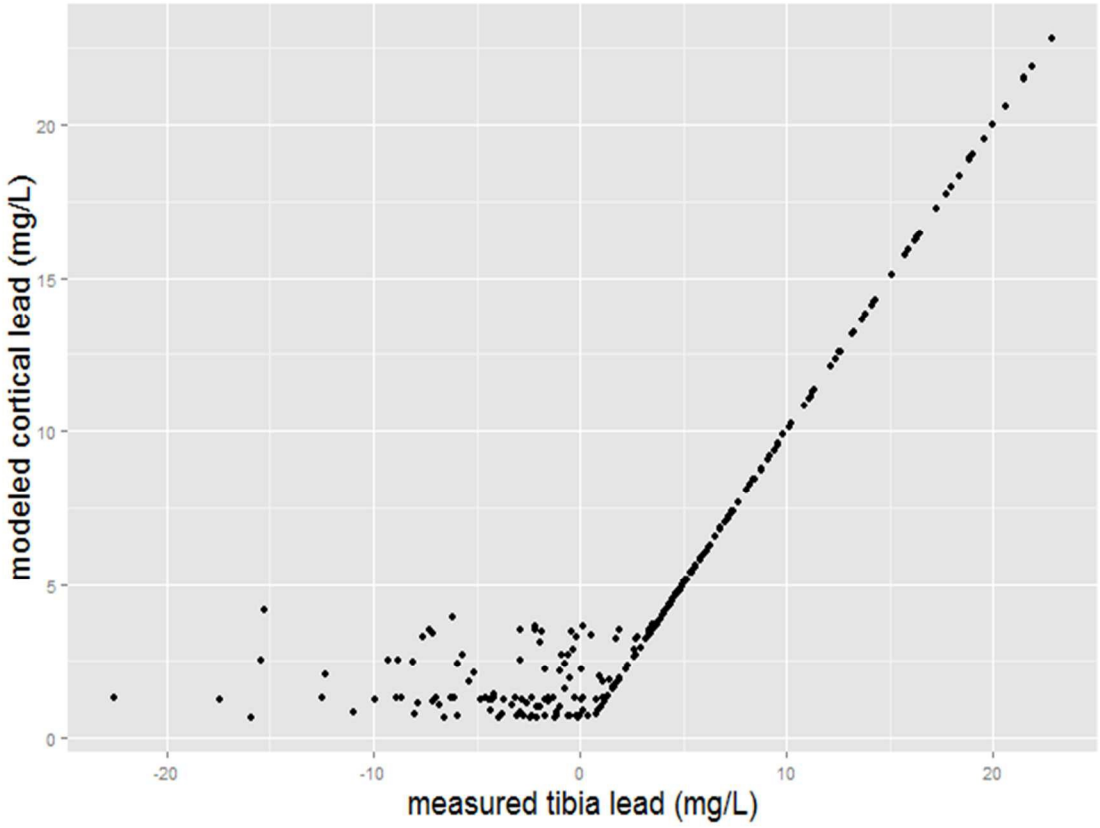

FIG. 4. Modeled cortical bone lead concentration as a function of measured tibia lead concentration.

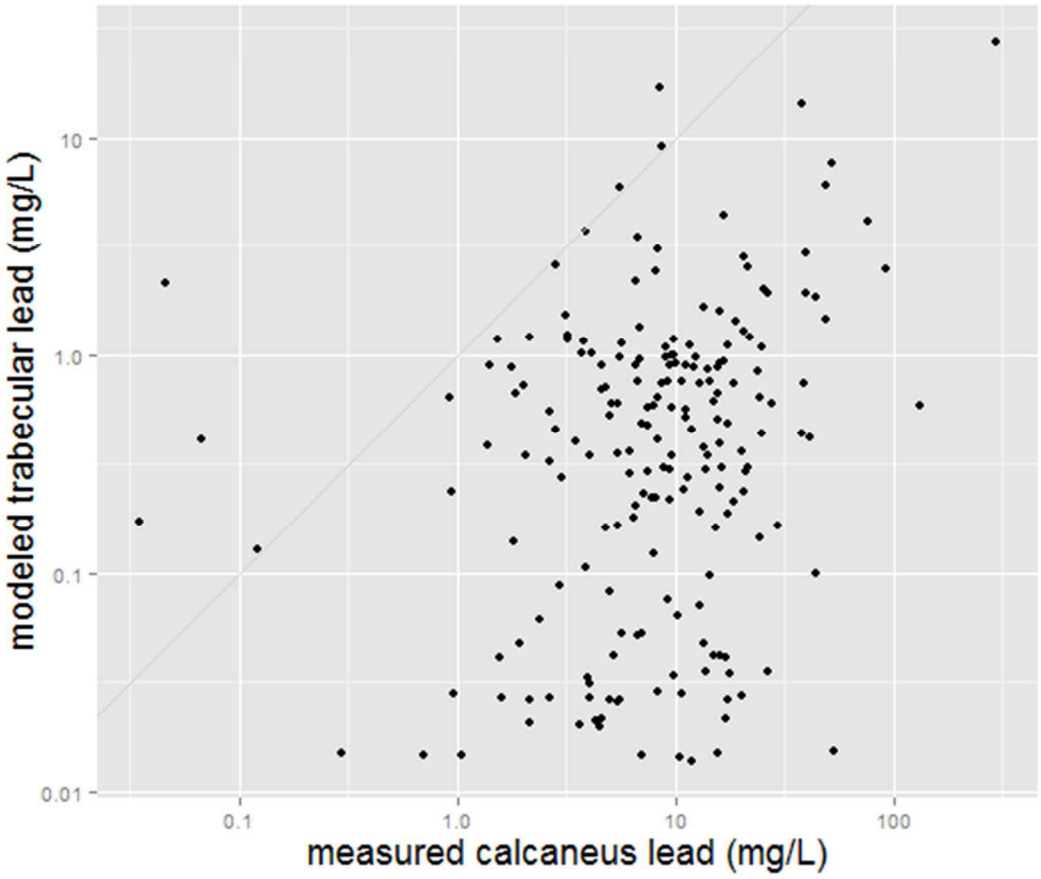

FIG. 5. Modeled trabecular bone lead concentration as a function of measured calcaneus lead concentration. To show the trend more clearly, the axis scales are presented in logarithmic form. Data are only shown for those points having measured calcaneus lead concentrations above 0 mg/L. The equation of best fit is $10^{y} = 10^{((0.33 \pm 0.09)\, x)} - 10^{((0.78 \pm 0.10))}$; $r^2 = 0.06$; $p < 0.001$

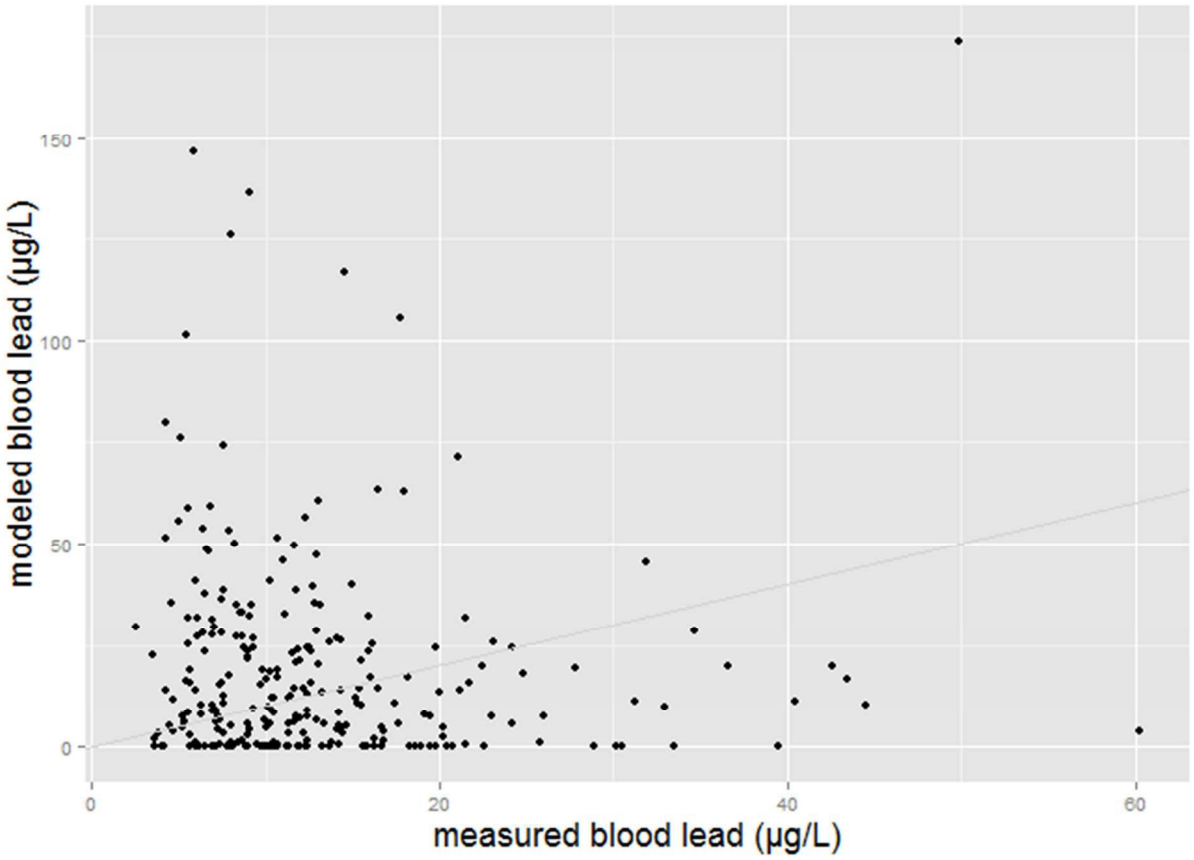

FIG. 6. Modeled blood lead concentration as a function of measured blood lead concentration. The equation of best fit is $y = (0.0 \pm 0.2)\ x + (19 \pm 3)$; $r^2 = 0.00$; $p = 0.89$

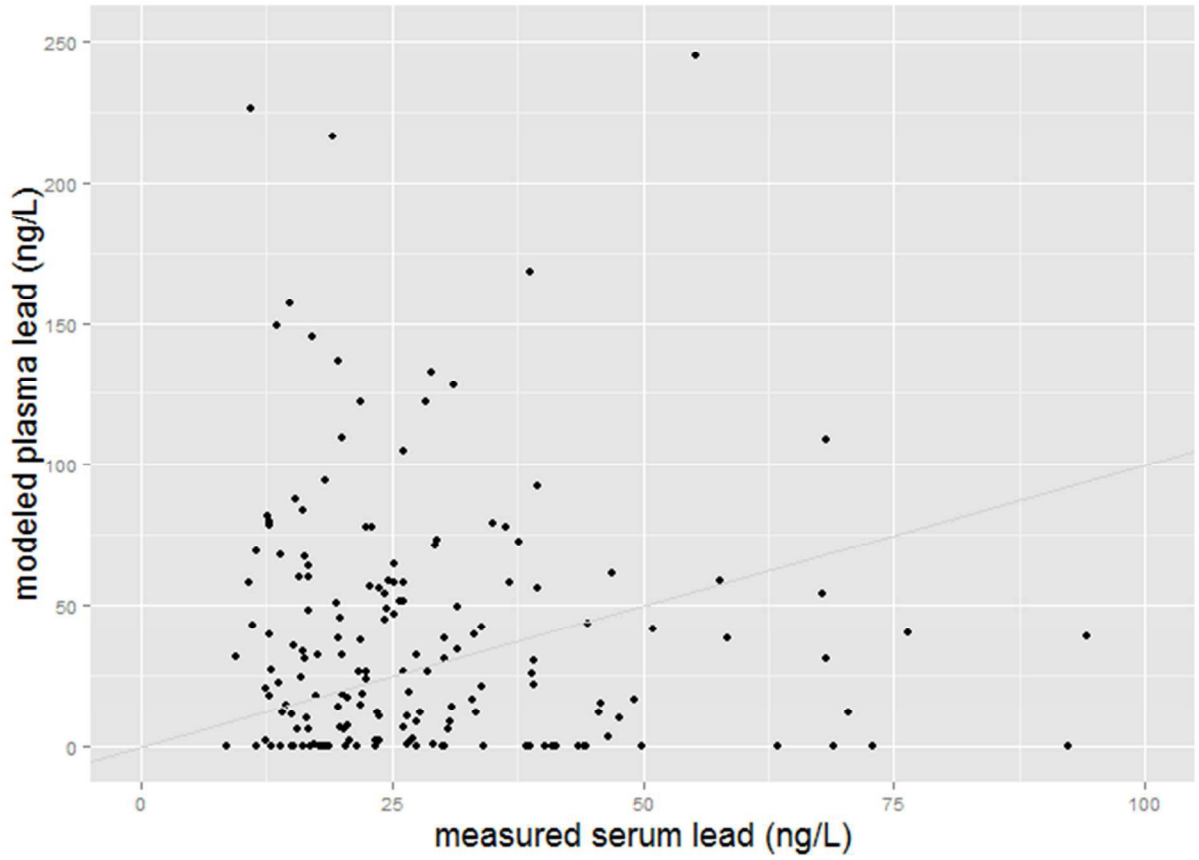

FIG. 7. Modeled plasma lead concentration as a function of measured serum lead concentration. For clarity, data are limited to modeled plasma lead concentrations < 250 ng/L and measured serum lead concentrations < 100 ng/L.
The equation of best fit is $y = (1.4 \pm 0.7)\ x + (25 \pm 27)$; $r^2 = 0.01$; $p = 0.06$

DISCUSSION

Nature of Results

The data shown in Figs. 5, 6, and 7 are highly scattered with no clear relationships between variables. In itself, this does not suggest that the revised model performed poorly. The model was meant to capture the general trends of observed lead concentrations for the population, not the exact lead distribution and body burden of individuals. In the absence of repeated lead measurements made over an individual's lifetime, it is highly unlikely that the model could be made to recreate individual results. The biological processes that move lead into and out of the body (and the various compartments within it) vary in rate over time and between individuals due to genetic and environmental factors, and the model cannot account for these individual differences. Instead, rates are approximated from age-dependent best-fit curves and average rates obtained from previous studies.[13] Furthermore, many sources of individual lead exposure could not be modeled accurately due to the absence of data for specific, and significant, changes in lead exposure throughout the lifetime. Although the model does allow input variables

to be changed in the middle of a simulation,[13] doing so accurately would require in-depth knowledge of lead exposure history for the individual. In the case of people with occupational lead exposure, such as the lead smelter workers analyzed in a previous study using this model,[6] such measurements may sometimes be accessible. However, for individuals such as those in this study, these measurements will simply not be available. The standard errors provided from measured values over the population (Table 2) demonstrate the high degree of variability within the data sets, with a particularly high relative standard error from tibia lead. Finally, uncertainties in individual-level measurements (bone, blood, and serum) can serve to complicate comparisons between measured and modeled lead levels on an individual level. However, by making comparisons over a large population, as is possible through this study, the effects of these individual-level variations can be minimized and model output can be evaluated for the larger population.

Treatment of Negative Output

When calibrating the model for certain participants with especially low measured tibia lead concentrations, matching the output for cortical bone lead concentration to these measurements resulted in negative output for the lead concentration in blood – and, often, trabecular bone – necessitating an alternate method of calibration for these participants, as negative concentrations are not physically possible (i.e. positive output values were required for CB, TCB, and CCB; see Methods). The model's ability to generate negative lead concentration output without negative lead exposure input suggests that one or more of its approximations of real human lead kinetics are not valid in unusually low lead exposure scenarios. The model manual [13] indicates that the total clearance of lead from the plasma to the kidneys (CL) is modeled as an age-dependent fraction of glomerular filtration rate (GFR), which itself is a function of body weight. Neither value is dependent on any lead concentration or exposure values. This approach is defended by noting that the glomerular filtration rate has generally been found not to be the rate-determining step for renal excretion of lead in individuals examined in previous lead exposure studies.[19,20] It is also noted, however, that this approach to capturing the glomerular filtration rate can only be assumed to be valid for individuals with blood lead concentrations that were typical in the 1990's and previous decades. The lowest blood lead concentrations observed in this study may not satisfy this condition. With a median observed blood lead concentration of 11 µg/L found in this study, many measured values fell below 10 µg/L, very low by recent historical standards. Given the equations used to model CL,[13] individuals with extremely low lead exposures could have been modeled as excreting more lead than they were modeled to have in their blood, resulting in negative blood lead concentrations. As such, an alternate approach to modeling renal excretion of lead is recommended to improve the modeling of lead metabolism in people with very low lead exposure histories. At least one previous study [21] also supports this conclusion, claiming that, although the O'Flaherty model should be able to capture human lead metabolism reasonably well when refined, its current

approach to simulating lead excretion may be inconsistent with observations of the age-dependence of human excretion kinetics, particularly in young children.

Tibia Lead

As can be seen in Fig. 4, the modeled cortical bone lead concentrations matched the positive observed tibia lead concentrations extremely well. However, this is not indicative of model accuracy, as the lead exposure input for each participant was specifically calibrated in order to match model cortical bone output to these observations (see Methods).

As noted, many of the observed tibia lead concentrations were negative. The corresponding subjects' cortical bone lead concentrations were modeled as positive in order to keep the model output physically realistic. Negative bone lead observations arose from measurement uncertainties inherent in the bone lead analysis. This effect is not unexpected when using bone lead X-ray fluorescence and will yield the occasional negative result, particularly in individuals with very low bone lead concentrations.[22] In addition to the errors arising from the X-ray fluorescence method, some high uncertainties were contributed from participants who were young children and could not remain motionless during bone lead measurement (with individual uncertainty ranging up to 34 μg/g). These high uncertainty measurements were, however, not typical. The mean tibia lead uncertainties, in units of μg Pb/g bone mineral, were 5.15 μg/g (standard error 0.22 μg/g) for females and 4.64 μg/g (standard error 0.28 μg/g) for males participating in this study.[12] For each individual's measurement, uncertainty was calculated based on a mathematical fitting of the participant's x-ray spectrum and from a set of calibration standards. Since tibia measurements were used in the individual model calibrations, any error in tibia concentration affected the model output for the other three tissue compartments (trabecular, blood, and serum concentrations). Uncertainties in tibia lead measurement were therefore the dominant source of uncertainty in making individual-level comparisons between observations and model output.

Calcaneus Lead

Overall, the model output for trabecular bone lead concentration was much lower than the observed calcaneus lead concentrations (see Fig. 5). A previous study [6] suggested that the calcaneus has a slower bone turnover rate than the trabecular bone compartment simulated by the O'Flaherty model. A more recent review [21] noted that trabecular bone lead kinetics may not be as different from cortical bone lead kinetics as assumed by the model in its current form. Accurate modeling of trabecular bone lead kinetics cannot be assumed from the model in its current form, and may require significant structural revision along the lines indicated immediately above.

Blood and Serum Lead

As can be seen from Figs. 6 and 7, the data for blood and serum lead are highly scattered; however, as shown in Table 2, the model was able to successfully capture the general trend of

the observations for the population as a whole. The discrepancy between the modeled/measured scatter in Figs. 6 and 7 on the one hand, and the good agreement between modeled/measured median results on the other, can be explained by a number of factors. As described above, these contributing factors are individual-level measurement uncertainties, variations within the population as a whole, and the nature of the tibia lead measurement results and their subsequent use to create modeled exposure histories.

From Fig. 8, it is clear that most study participants were modeled as having one of two distinct ratios of blood lead to cortical bone lead. Analysis of the data revealed that the higher of these two ratios generally corresponded to younger participants (<13 years of age), while the lower generally corresponded to adults (>20 years of age) with very low modeled lead exposure. In the case of the younger participants, this constant ratio between blood lead and cortical lead is a consequence of relatively high bone turnover rates – as observed bone lead goes up, blood lead must increase in a nearly linear fashion in order to maintain the necessary transfer of lead to bone. In the case of adults with low lead exposure, the distinct lower ratio between blood lead and cortical lead is an artifact of historically modeled exposure levels. Since these individuals were mostly modeled as having minimal current lead exposure, their contributions to bone lead stores were driven entirely by exposure in the past. This, in turn, means that current blood lead is directly dependent on endogenous (internal) exposure from bone, and the resulting current blood lead levels scale directly with current bone lead. The remainder of the modeled population fell somewhere in between these two distinct ratios of blood lead to cortical bone lead, and represented intermediate cases between young participants and low-exposure adults. Overall, the majority of non-negative measured tibia lead data points fell in between these two distinct modeled ratios. The agreement between the linear fit for measured blood lead vs. tibia lead and modeled blood lead vs. cortical bone lead as presented in Fig. 8 was not good. This can be attributed to the retention of negative tibia lead values in the measured data set, and the emergence of a distinctive bifurcation of results in the modeled data set.

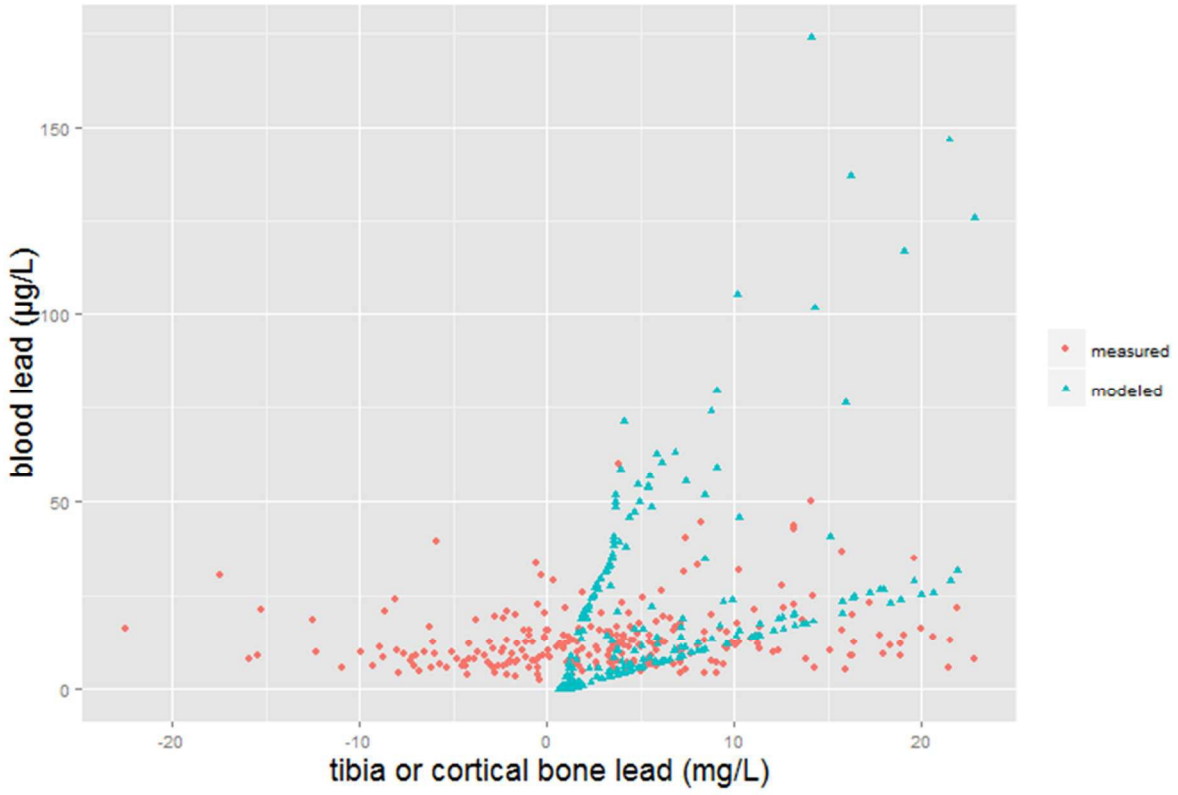

FIG. 8. Measured or modeled blood lead concentration as a function of measured or modeled cortical bone (tibia) lead concentration. The equation of best fit from the measured data is $y = (0.21 \pm 0.07)\ x + (12.3 \pm 0.6)$; $r^2 = 0.03$; $p < 0.01$. The equation of best fit from the modeled data is $y = (2.5 \pm 0.3)\ x + (6 \pm 2)$; $r^2 = 0.25$; $p < 0.001$.

Conclusion

Using data obtained from a sample of people living in the Greater Toronto Area, the O'Flaherty model of lead kinetics has been tested and refined for applicability to contemporary human populations with low, chronic lead exposure histories. After revision of modeled blood lead binding constants and the model input parameter for lead clearance from blood to bone, adjusting the modeled lead exposure history for each individual (to match the output of cortical lead concentration to measured tibia lead concentration) allowed the model to capture the general trends of observed blood and serum lead concentrations at the population level. The median observed blood lead concentration was 11 µg/L, and the median modeled concentration was 11 µg/L. The median observed serum lead concentration was 24 ng/L, and the median modeled concentration was 22 ng/L. This was a considerable improvement over results obtained using the original model (39 µg/L and 95 ng/L, respectively). However, the model was not able to simulate observed patterns in trabecular bone lead concentration, or to reproduce measured lead distributions in individuals. With the revisions introduced through this study, the model should be a useful tool in the analysis of human lead kinetics and body burden in populations characterized by low, chronic exposure to lead from the general environment.

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